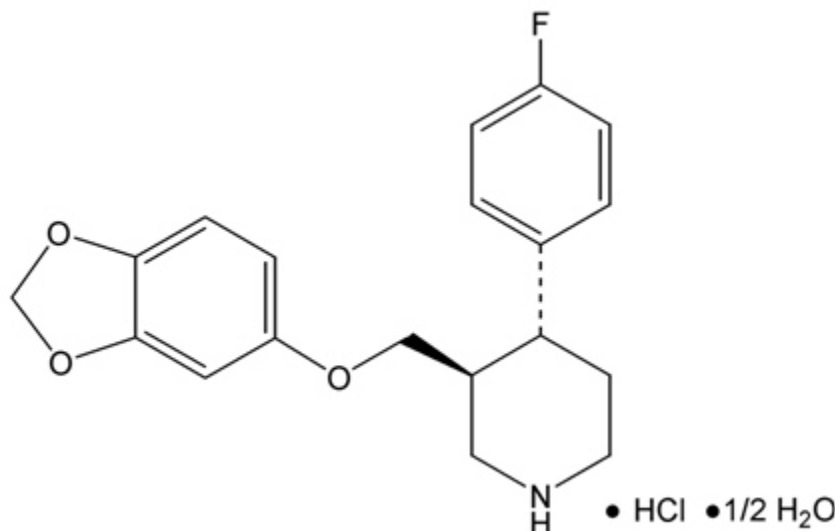


SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of paroxetine or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Paroxetine is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRECAUTIONS: Pediatric Use.)

DESCRIPTION

Paroxetine hydrochloride extended-release tablets are an orally administered psychotropic drug with a chemical structure unrelated to other selective serotonin reuptake inhibitors or to tricyclic, tetracyclic or other available antidepressant or antipanic agents. It is the hydrochloride salt of a phenylpiperidine compound identified chemically as (3S-trans)-3-[(1,3-benzodioxol-5-yloxy)methyl]-4-(4-fluorophenyl)-piperidine hydrochloride hemihydrate and has the molecular formula of $C_{19}H_{20}FNO_3 \cdot HCl \cdot \frac{1}{2} H_2O$. The molecular weight is 374.8 (329.4 as free base). The structural formula of paroxetine hydrochloride is:



Paroxetine hydrochloride (hemihydrate), USP is an odorless, white to almost white crystalline powder, having a melting point range of 120° to 138°C and a solubility of 5.4 mg/mL in water.

Each enteric film-coated, extended-release tablet contains paroxetine hydrochloride hemihydrate equivalent to 12.5 mg or 25 mg paroxetine. Inactive ingredients consist of colloidal silicon dioxide, hydroxypropyl cellulose, hypromellose, lactose monohydrate, magnesium stearate, methacrylic acid copolymer type C, microcrystalline cellulose, polydextrose, polyethylene glycol, polysorbate 80, sodium hydroxide, talc, titanium dioxide, triacetin and triethyl citrate. In addition, the 25 mg product contains the following coloring agents: D&C Red No. 30 Aluminum Lake, FD&C Blue No. 2 Aluminum Lake, FD&C Yellow No. 6 Aluminum Lake. In addition, paroxetine hydrochloride extended-release tablets may also contain imprinting ink consisting of either black pigment and natural resin or black iron oxide and propylene glycol.

Paroxetine hydrochloride complies with *USP Chromatographic Purity Test 1*.

CLINICAL PHARMACOLOGY

Pharmacodynamics

The efficacy of paroxetine in the treatment of major depressive disorder, panic disorder, social anxiety disorder and premenstrual dysphoric disorder (PMDD) is presumed to be linked to potentiation of serotonergic activity in the central nervous system resulting from inhibition of neuronal reuptake of serotonin (5-hydroxy-tryptamine, 5-HT). Studies at clinically relevant doses in humans have demonstrated that paroxetine blocks the uptake of serotonin into human platelets. *In vitro* studies in animals also suggest that paroxetine is a potent and highly selective inhibitor of neuronal serotonin reuptake and has only very weak effects on norepinephrine

and dopamine neuronal reuptake. *In vitro* radioligand binding studies indicate that paroxetine has little affinity for muscarinic, α_1 -, α_2 -, beta-adrenergic-, dopamine (D_2)-, 5-HT $_1$ -, 5-HT $_2$ - and histamine (H_1)-receptors; antagonism of muscarinic, histaminergic and α_1 -adrenergic receptors has been associated with various anticholinergic, sedative and cardiovascular effects for other psychotropic drugs.

Because the relative potencies of paroxetine's major metabolites are at most 1/50 of the parent compound, they are essentially inactive.

Pharmacokinetics

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. The elimination half-life is approximately 15 to 20 hours after a single dose of paroxetine hydrochloride extended-release tablets. Paroxetine is extensively metabolized and the metabolites are considered to be inactive. Nonlinearity in pharmacokinetics is observed with increasing doses. Paroxetine metabolism is mediated in part by CYP2D6 and the metabolites are primarily excreted in the urine and to some extent in the feces. Pharmacokinetic behavior of paroxetine has not been evaluated in subjects who are deficient in CYP2D6 (poor metabolizers).

Absorption and Distribution

Paroxetine hydrochloride is completely absorbed after oral dosing of a solution of the hydrochloride salt. In a study in which normal male and female subjects ($n = 23$) received single oral doses of paroxetine hydrochloride extended-release tablets at four dosage strengths (12.5 mg, 25 mg, 37.5 mg and 50 mg), paroxetine C_{max} and AUC_{0-inf} increased disproportionately with dose (as seen also with immediate-release formulations). Mean C_{max} and AUC_{0-inf} values at these doses were 2, 5.5, 9 and 12.5 ng/mL and 121, 261, 338 and 540 ng•hr/mL, respectively. T_{max} was observed typically between 6 and 10 hours post-dose, reflecting a reduction in absorption rate compared with immediate-release formulations. The bioavailability of 25 mg paroxetine hydrochloride extended-release tablets is not affected by food.

Paroxetine distributes throughout the body, including the CNS, with only 1% remaining in the plasma.

Approximately 95% and 93% of paroxetine is bound to plasma protein at 100 ng/mL and 400 ng/mL, respectively. Under clinical conditions, paroxetine concentrations would normally be less than 400 ng/mL. Paroxetine does not alter the *in vitro* protein binding of phenytoin or warfarin.

Metabolism and Excretion

The mean elimination half-life of paroxetine was 15 to 20 hours throughout a range of single doses of paroxetine hydrochloride extended-release tablets (12.5 mg, 25 mg, 37.5 mg and 50 mg). During repeated administration of paroxetine hydrochloride extended-release tablets (25 mg once daily), steady-state was reached within 2 weeks (i.e., comparable to immediate-release formulations). In a repeat dose study in which normal male and female subjects ($n = 23$) received paroxetine hydrochloride extended-release tablets (25 mg daily), mean steady-state C_{max} , C_{min} and AUC_{0-24} values were 30 ng/mL, 20 ng/mL and 550 ng•hr/mL, respectively.

Based on studies using immediate-release formulations, steady-state drug exposure based on AUC_{0-24} was several-fold greater than would have been predicted from single-dose data. The excess accumulation is a consequence of the fact that one of the enzymes that metabolizes paroxetine is readily saturable.

In steady-state dose proportionality studies involving elderly and nonelderly patients, at doses of the immediate-release formulation of 20 mg to 40 mg daily for the elderly and 20 mg to 50 mg daily for the nonelderly, some nonlinearity was observed in both populations, again reflecting a saturable metabolic pathway. In comparison to C_{min} values after 20 mg daily, values after 40 mg daily were only about 2 to 3 times greater than doubled.

Paroxetine is extensively metabolized after oral administration. The principal metabolites are polar and conjugated products of oxidation and methylation, which are readily cleared. Conjugates with glucuronic acid and sulfate predominate and major metabolites have been isolated and identified. Data indicate that the metabolites have no more than 1/50 the potency of the parent compound at inhibiting serotonin uptake. The metabolism of paroxetine is accomplished in part by CYP2D6. Saturation of this enzyme at clinical doses appears to account for the nonlinearity of paroxetine kinetics with increasing dose and increasing duration of treatment. The role of this enzyme in paroxetine metabolism also suggests potential drug-drug interactions (see PRECAUTIONS).

Approximately 64% of a 30 mg oral solution dose of paroxetine was excreted in the urine with 2% as the parent compound and 62% as metabolites over a 10 day post-dosing period. About 36% was excreted in the feces (probably via the bile), mostly as metabolites and less than 1% as the parent compound over the 10 day post-dosing period.

Other Clinical Pharmacology Information

Specific Populations

Renal and Liver Disease

Increased plasma concentrations of paroxetine occur in subjects with renal and hepatic impairment. The mean plasma concentrations in patients with creatinine clearance below 30 mL/min was approximately 4 times greater than seen in normal volunteers. Patients with creatinine clearance of 30 to 60 mL/min and patients with hepatic functional impairment had about a 2-fold increase in plasma concentrations (AUC, C_{max}).

The initial dosage should therefore be reduced in patients with severe renal or hepatic impairment and upward titration, if necessary, should be at increased intervals (see DOSAGE AND ADMINISTRATION).

Elderly Patients

In a multiple-dose study in the elderly at daily doses of 20 mg, 30 mg and 40 mg of the immediate-release formulation, C_{min} concentrations were about 70% to 80% greater than the respective C_{min} concentrations in nonelderly subjects. Therefore the initial dosage in the elderly should be reduced (see DOSAGE AND ADMINISTRATION).

Drug-Drug Interactions

In vitro drug interaction studies reveal that paroxetine inhibits CYP2D6. Clinical drug interaction studies have been performed with substrates of CYP2D6 and show that paroxetine can inhibit the metabolism of drugs metabolized by CYP2D6 including desipramine, risperidone and atomoxetine (see PRECAUTIONS: Drug Interactions).

Clinical Trials

Major Depressive Disorder

The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for major depressive disorder has been established in two 12 week, flexible dose, placebo-controlled studies of patients with DSM-IV Major Depressive Disorder. One study included patients in the age range 18 to 65 years and a second study included elderly patients, ranging in age from 60 to 88. In both studies, paroxetine hydrochloride extended-release tablets were shown to be significantly more effective than placebo in treating major depressive disorder as measured by the following: Hamilton Depression Rating Scale (HDRS), the Hamilton depressed mood item and the Clinical Global Impression (CGI)–Severity of Illness score.

A study of outpatients with major depressive disorder who had responded to immediate-release paroxetine tablets (HDRS total score < 8) during an initial 8 week open treatment phase and were then randomized to continuation on immediate-release paroxetine tablets or placebo for one year demonstrated a significantly lower relapse rate for patients taking immediate-release paroxetine tablets (15%) compared to those on placebo (39%). Effectiveness was similar for male and female patients.

Panic Disorder

The effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of panic disorder was evaluated in three 10 week, multicenter, flexible dose studies (Studies 1, 2 and 3) comparing paroxetine extended-release tablets (12.5 mg to 75 mg daily) to placebo in adult outpatients who had panic disorder (DSM-IV), with or without agoraphobia. These trials were assessed on the basis of their outcomes on three variables: (1) the proportions of patients free of full panic attacks at endpoint; (2) change from baseline to endpoint in the median number of full panic attacks; and (3) change from baseline to endpoint in the median Clinical Global Impression Severity score. For Studies 1 and 2, paroxetine hydrochloride extended-release tablets were consistently superior to placebo on 2 of these 3 variables. Study 3 failed to consistently demonstrate a significant difference between paroxetine hydrochloride extended-release tablets and placebo on any of these variables.

For all three studies, the mean dose of paroxetine hydrochloride extended-release tablets for completers at endpoint was approximately 50 mg/day. Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of age or gender.

Long-term maintenance effects of the immediate-release formulation of paroxetine in panic disorder were demonstrated in an extension study. Patients who were responders during a 10 week double-blind phase with immediate-release paroxetine and during a 3 month double-blind extension phase were randomized to either immediate-release paroxetine or placebo in a 3 month double-blind relapse prevention phase. Patients randomized to paroxetine were significantly less likely to relapse than comparably treated patients who were randomized to placebo.

Social Anxiety Disorder

The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of social anxiety disorder was demonstrated in

a 12 week, multicenter, double-blind, flexible dose, placebo-controlled study of adult outpatients with a primary diagnosis of social anxiety disorder (DSM-IV). In the study, the effectiveness of paroxetine hydrochloride extended-release tablets (12.5 mg to 37.5 mg daily) compared to placebo was evaluated on the basis of (1) change from baseline in the Liebowitz Social Anxiety Scale (LSAS) total score and (2) the proportion of responders who scored 1 or 2 (very much improved or much improved) on the Clinical Global Impression (CGI) Global Improvement score.

Paroxetine hydrochloride extended-release tablets demonstrated statistically significant superiority over placebo on both the LSAS total score and the CGI Improvement responder criterion. For patients who completed the trial, 64% of patients treated with paroxetine hydrochloride extended-release tablets compared to 34.7% of patients treated with placebo were CGI Improvement responders.

Subgroup analyses did not indicate that there were any differences in treatment outcomes as a function of gender. Subgroup analyses of studies utilizing the immediate-release formulation of paroxetine generally did not indicate differences in treatment outcomes as a function of age, race or gender.

Premenstrual Dysphoric Disorder

The effectiveness of paroxetine hydrochloride extended-release tablets for the treatment of PMDD utilizing a continuous dosing regimen has been established in two placebo-controlled trials. Patients in these trials met DSM-IV criteria for PMDD. In a pool of 1,030 patients, treated with daily doses of paroxetine hydrochloride extended-release tablets 12.5 or 25 mg/day or placebo the mean duration of the PMDD symptoms was approximately 11 ± 7 years. Patients on systemic hormonal contraceptives were excluded from these trials. Therefore, the efficacy of paroxetine hydrochloride extended-release tablets in combination with systemic (including oral) hormonal contraceptives for the continuous daily treatment of PMDD is unknown. In both positive studies, patients (n = 672) were treated with 12.5 mg/day or 25 mg/day of paroxetine hydrochloride extended-release tablets or placebo continuously throughout the menstrual cycle for a period of 3 menstrual cycles. The VAS-Total score is a patient-rated instrument that mirrors the diagnostic criteria of PMDD as identified in the DSM-IV and includes assessments for mood, physical symptoms and other symptoms. 12.5 mg/day and 25 mg/day of paroxetine hydrochloride extended-release tablets were significantly more effective than placebo as measured by change from baseline to the endpoint on the luteal phase VAS-Total score.

In a third study employing intermittent dosing, patients (n = 366) were treated for the 2 weeks prior to the onset of menses (luteal phase dosing, also known as intermittent dosing) with 12.5 mg/day or 25 mg/day of paroxetine hydrochloride extended-release tablets or placebo for a period of 3 months. 12.5 mg/day and 25 mg/day of paroxetine hydrochloride extended-release tablets, as luteal phase dosing, was significantly more effective than placebo as measured by change from baseline luteal phase VAS total score.

There is insufficient information to determine the effect of race or age on outcome in these studies.

INDICATIONS AND USAGE

Major Depressive Disorder

Paroxetine hydrochloride extended-release tablets are indicated for the treatment of major depressive disorder.

The efficacy of paroxetine hydrochloride extended-release tablets in the treatment of a major depressive episode was established in two 12 week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning and includes the presence of at least 5 of the following 9 symptoms during the same 2 week period: Depressed mood, markedly diminished interest or pleasure in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

Paroxetine hydrochloride extended-release tablets have not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to one year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials). The physician who elects to use paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Panic Disorder

Paroxetine hydrochloride extended-release tablets are indicated for the treatment of panic disorder, with or without agoraphobia, as defined in DSM-IV. Panic disorder is characterized by the occurrence of unexpected panic attacks and associated concern about having additional attacks, worry about the implications or consequences of the attacks and/or a significant change in behavior related to the attacks.

The efficacy of paroxetine hydrochloride extended-release tablets was established in two 10 week trials in panic disorder patients whose diagnoses corresponded to the DSM-IV category of panic disorder (see CLINICAL PHARMACOLOGY: Clinical Trials).

Panic disorder (DSM-IV) is characterized by recurrent unexpected panic attacks, i.e., a discrete period of intense fear or discomfort in which four (or more) of the following symptoms develop abruptly and reach a peak within 10 minutes: (1) palpitations, pounding heart or accelerated heart rate; (2) sweating; (3) trembling or shaking; (4) sensations of shortness of breath or smothering; (5) feeling of choking; (6) chest pain or discomfort; (7) nausea or abdominal distress; (8) feeling dizzy, unsteady, lightheaded or faint; (9) derealization (feelings of unreality) or depersonalization (being detached from oneself); (10) fear of losing control; (11) fear of dying; (12) paresthesias (numbness or tingling sensations); (13) chills or hot flushes.

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3 month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo (see CLINICAL PHARMACOLOGY: Clinical Trials). Nevertheless, the physician who prescribes paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

Social Anxiety Disorder

Paroxetine hydrochloride extended-release tablets are indicated for the treatment of social anxiety disorder, also known as social phobia, as defined in DSM-IV (300.23). Social anxiety disorder is characterized by a marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. Exposure to the feared situation almost invariably provokes anxiety, which may approach the intensity of a panic attack. The feared situations are avoided or endured with intense anxiety or distress. The avoidance, anxious anticipation or distress in the feared situation(s) interferes significantly with the person's normal routine, occupational or academic functioning or social activities or relationships or there is marked distress about having the phobias. Lesser degrees of performance anxiety or shyness generally do not require psychopharmacological treatment.

The efficacy of paroxetine hydrochloride extended-release tablets as a treatment for social anxiety disorder has been established, in part, on the basis of extrapolation from the established effectiveness of the immediate-release formulation of paroxetine. In addition, the efficacy of paroxetine hydrochloride extended-release tablets was established in a 12 week trial, in adult outpatients with social anxiety disorder (DSM-IV). Paroxetine hydrochloride extended-release tablets have not been studied in children or adolescents with social phobia (see CLINICAL PHARMACOLOGY: Clinical Trials).

The effectiveness of paroxetine hydrochloride extended-release tablets in long-term treatment of social anxiety disorder, i.e., for more than 12 weeks, has not been systematically evaluated in adequate and well controlled trials. Therefore, the physician who elects to prescribe paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient (see DOSAGE AND ADMINISTRATION).

Premenstrual Dysphoric Disorder

Paroxetine hydrochloride extended-release tablets are indicated for the treatment of PMDD.

The efficacy of paroxetine hydrochloride extended-release tablets in the treatment of PMDD has been established in 3 placebo-controlled trials (see CLINICAL PHARMACOLOGY: Clinical Trials).

The essential features of PMDD, according to DSM-IV, include markedly depressed mood, anxiety or tension, affective lability and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. These symptoms occur regularly during the luteal phase and remit within a few days following the onset of menses; the disturbance markedly interferes with work or school or with usual social activities and relationships with others. In making the diagnosis, care should be taken to rule out other cyclical mood disorders that may be exacerbated by treatment with an antidepressant.

The effectiveness of paroxetine hydrochloride extended-release tablets in long-term use, that is, for more than three menstrual cycles, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs), including linezolid, an antibiotic which is a reversible nonselective MAOI or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paroxetine hydrochloride extended-release tablets are contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in paroxetine hydrochloride extended-release tablets.

WARNINGS

Clinical Worsening and Suicide Risk

Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other

psychiatric disorders and these disorders themselves are the strongest predictors of suicide. There has been a longstanding concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents and young adults (ages 18 to 24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD) or other psychiatric disorders included a total of 24 short-term trials of nine antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1,000 Patients Treated
Increases Compared to Placebo	
< 18	14 additional cases
18 to 24	5 additional cases
Decreases Compared to Placebo	
25 to 64	1 fewer case
≥ 65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide.

It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression.

All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially during the initial few months of a course of drug therapy or at times of dose changes, either increases or decreases.

The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality.

Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset or were not part of the patient's presenting symptoms.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms (see PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets, for a description of the risks of discontinuation of paroxetine).

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior and the other symptoms described above, as well as the emergence of suicidality and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder

A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is

unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression. It should be noted that paroxetine is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors

In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine hydrochloride extended-release tablets not be used in combination with an MAOI (including linezolid, an antibiotic which is a reversible nonselective MAOI) or within 14 days of discontinuing treatment with an MAOI (see CONTRAINDICATIONS). At least 2 weeks should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-Like Reactions

The development of a potentially life threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including paroxetine hydrochloride extended-release tablet treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs) or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of paroxetine hydrochloride extended-release tablets with MAOIs intended to treat depression is contraindicated.

If concomitant treatment of paroxetine hydrochloride extended-release tablets with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases.

The concomitant use of paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended.

Treatment with paroxetine hydrochloride extended-release tablets and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Potential Interaction with Thioridazine

Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as Torsade de pointes type arrhythmias and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine.

Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy

Teratogenic Effects

Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: General: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1 to 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8 to 2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings

Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on an mg/m² basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on an mg/m² basis. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects

Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective case control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately 6-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk.

There have also been post-marketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment (see DOSAGE AND ADMINISTRATION). Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication.

PRECAUTIONS

General

Activation of Mania/Hypomania

During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder or PMDD treated with paroxetine hydrochloride extended-release tablets in controlled clinical studies, there were no reports of mania or hypomania.

As with all drugs effective in the treatment of major depressive disorder, paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of mania.

Seizures

During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine-treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received paroxetine hydrochloride extended-release tablets in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder or PMDD, one patient (0.1%) experienced a seizure. Paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets

Adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of paroxetine hydrochloride extended-release tablets up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for one week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for paroxetine hydrochloride extended-release tablets, at an incidence of 2% or greater for paroxetine hydrochloride extended-release tablets and were at least twice that reported for placebo: Dizziness, nausea, nervousness and additional symptoms described by the investigator as associated with tapering or discontinuing paroxetine hydrochloride extended-release tablets (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with paroxetine hydrochloride extended-release tablets.

During marketing of paroxetine hydrochloride extended-release tablets and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, (particularly when abrupt), including the following: Dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations and tinnitus), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. While these events are generally self limiting, there have been reports of serious discontinuation symptoms.

Patients should be monitored for these symptoms when discontinuing treatment with paroxetine hydrochloride extended-release tablets. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate (see DOSAGE AND ADMINISTRATION).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia

The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia

Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including paroxetine hydrochloride extended-release tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk (see Geriatric Use). Discontinuation of paroxetine hydrochloride extended-release tablets should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest and death.

Abnormal Bleeding

SSRIs and SNRIs, including paroxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin and other anticoagulants may add to this risk. Case reports and epidemiological studies (case control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis and

petechiae to life threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of paroxetine and NSAIDs, aspirin or other drugs that affect coagulation.

Use in Patients with Concomitant Illness

Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine hydrochloride extended-release tablets in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine hydrochloride extended-release tablets are prescribed for patients with narrow angle glaucoma.

Paroxetine hydrochloride extended-release tablets or the immediate-release formulation has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Information for Patients

Paroxetine hydrochloride extended-release tablets should not be chewed or crushed and should be swallowed whole.

Patients should be cautioned about the risk of serotonin syndrome with the concomitant use of paroxetine and triptans, tramadol or other serotonergic agents.

Prescribers or other health professionals should inform patients, their families and their caregivers about the benefits and risks associated with treatment with paroxetine and should counsel them in its appropriate use. A patient Medication Guide about “Antidepressant Medicines, Depression and other Serious Mental Illness and Suicidal Thoughts or Actions” is available for paroxetine. The prescriber or health professional should instruct patients, their families and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking paroxetine.

Clinical Worsening and Suicide Risk

Patients, their families and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day to day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication.

Drugs That Interfere with Hemostasis (e.g., NSAIDs, Aspirin and Warfarin)

Patients should be cautioned about the concomitant use of paroxetine and NSAIDs, aspirin, warfarin or other drugs that affect coagulation since the combined use of psychotropic drugs that interfere with serotonin reuptake and these agents has been associated with an increased risk of bleeding.

Interference with Cognitive and Motor Performance

Any psychoactive drug may impair judgment, thinking or motor skills. Although in controlled studies immediate-release paroxetine hydrochloride has not been shown to impair psychomotor performance, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with paroxetine hydrochloride extended-release tablets does not affect their ability to engage in such activities.

Completing Course of Therapy

While patients may notice improvement with use of paroxetine hydrochloride extended-release tablets in 1 to 4 weeks, they should be advised to continue therapy as directed.

Concomitant Medications

Patients should be advised to inform their physician if they are taking or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions.

Alcohol

Although immediate-release paroxetine hydrochloride has not been shown to increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine hydrochloride extended-release tablets.

Pregnancy

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy (see WARNINGS: Usage in Pregnancy: Teratogenic and Nonteratogenic Effects).

Nursing

Patients should be advised to notify their physician if they are breast-feeding an infant (see PRECAUTIONS: Nursing Mothers).

Laboratory Tests

There are no specific laboratory tests recommended.

Drug Interactions

Tryptophan

As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of paroxetine hydrochloride extended-release tablets with tryptophan is not recommended (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: Serotonin Syndrome).

Monoamine Oxidase Inhibitors

See CONTRAINDICATIONS and WARNINGS.

Pimozide

In a controlled study of healthy volunteers, after immediate-release paroxetine hydrochloride was titrated to 60 mg daily, coadministration of a single-dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. The increase in pimozide AUC and C_{max} is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine hydrochloride extended-release tablets are contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs

Based on the mechanism of action of SNRIs and SSRIs, including paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible nonselective MAOI), lithium, tramadol or St. John's Wort (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: Serotonin Syndrome). The concomitant use of paroxetine extended-release tablets with MAOIs (including linezolid) is contraindicated (see CONTRAINDICATIONS). The concomitant use of paroxetine extended-release tablets with other SSRI's, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions: Tryptophan).

Thioridazine

See CONTRAINDICATIONS and WARNINGS.

Warfarin

Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine hydrochloride extended-release tablets and warfarin should be undertaken with caution (see PRECAUTIONS: Information for Patients: Drugs That Interfere with Hemostasis).

Triptans

There have been rare post-marketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: Serotonin Syndrome).

Drugs Affecting Hepatic Metabolism

The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug-metabolizing enzymes.

Cimetidine

Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine hydrochloride extended-release tablets after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital

Phenobarbital induces many cytochrome P₄₅₀ (oxidative) enzymes. When a single oral 30 mg dose of immediate-release paroxetine was administered at phenobarbital steady-state (100 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the two drugs are both being chronically dosed. No initial dosage adjustment with paroxetine hydrochloride extended-release tablets is considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin

When a single oral 30 mg dose of immediate-release paroxetine was administered at phenytoin steady-state (300 mg once daily for 14 days), paroxetine AUC and T_{1/2} were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady-state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the two drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when paroxetine hydrochloride extended-release tablets are coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS: Post-marketing Reports).

Drugs Metabolized by CYP2D6

Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs and many tricyclics), are metabolized by the cytochrome P₄₅₀ isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (> 90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In one study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single dose desipramine (100 mg) C_{max}, AUC and T_{1/2} by an average of approximately 2-, 5- and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In one study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxyrisperidone concentrations approximately 10% and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady-state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of paroxetine hydrochloride extended-release tablets with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may require lower doses than usually prescribed for either paroxetine hydrochloride extended-release tablets or the other drug.

Therefore, coadministration of paroxetine hydrochloride extended-release tablets with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine and fluoxetine), phenothiazines, risperidone, tamoxifen and Type 1C antiarrhythmics (e.g., propafenone, flecainide and encainide) or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

Tamoxifen is a prodrug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite and hence reduced efficacy of tamoxifen.

At steady-state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by alternative P₄₅₀ isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS: Drug Interactions: Tricyclic Antidepressants).

Drugs Metabolized by Cytochrome CYP3A4

An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs)

Caution is indicated in the coadministration of TCAs with paroxetine hydrochloride extended-release tablets, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored and the dose of TCA may need to be reduced, if a TCA is coadministered with paroxetine hydrochloride extended-release tablets (see PRECAUTIONS: Drug Interactions: Drugs Metabolized by Cytochrome CYP2D6).

Drugs Highly Bound to Plasma Protein

Because paroxetine is highly bound to plasma protein, administration of paroxetine hydrochloride extended-release tablets to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere with Hemostasis (e.g., NSAIDs, Aspirin and Warfarin)

Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

Alcohol

Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine hydrochloride extended-release tablets.

Lithium

A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

Digoxin

The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady-state. Mean digoxin AUC at steady-state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine hydrochloride extended-release tablets and digoxin should be undertaken with caution.

Diazepam

Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine

Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state AUC₀₋₂₄, C_{max} and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37% and 67%, respectively, compared to procyclidine alone at steady-state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers

In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Post-marketing Reports).

Theophylline

Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir

Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT)

There are no clinical studies of the combined use of ECT and paroxetine hydrochloride extended-release tablets.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Two year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5 and 25 mg/kg/day (mice) and 1, 5 and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the (MRHD) on a mg/m² basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50 and 4/50 for control, low-, middle- and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose related increase in the number of tumors in mice, there was no drug-related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis

Paroxetine produced no genotoxic effects in a battery of five *in vitro* and two *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility

A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m² basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m² basis).

Pregnancy

Pregnancy Category D

See WARNINGS: Usage in Pregnancy: Teratogenic and Nonteratogenic Effects.

Labor and Delivery

The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers

Like many other drugs, paroxetine is secreted in human milk and caution should be exercised when paroxetine hydrochloride extended-release tablets are administered to a nursing woman.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine hydrochloride and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine hydrochloride extended-release tablets in a child or adolescent must balance the potential risks with the clinical need. In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self harm, suicidal thoughts, attempted suicide, crying and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes and tearfulness), nervousness, dizziness, nausea and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets).

Geriatric Use

SSRIs and SNRIs, including paroxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS: Hyponatremia).

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, paroxetine hydrochloride extended-release tablets were demonstrated to be safe and effective in the treatment of elderly patients (> 60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY: Clinical Trials and ADVERSE REACTIONS: Table 3.)

ADVERSE REACTIONS

The information included under the “Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paroxetine Hydrochloride Extended-Release Tablets” subsection of ADVERSE REACTIONS is based on data from eleven placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder, one study was conducted in patients with social anxiety disorder and four studies were done in female patients with PMDD. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies and the information from the PMDD studies. Information on additional adverse events associated with paroxetine hydrochloride extended-release tablets and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During the Clinical Development of Paroxetine).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paroxetine Hydrochloride Extended-Release Tablets

Adverse Events Associated With Discontinuation of Treatment

Major Depressive Disorder

Ten percent (21/212) of patients treated with paroxetine hydrochloride extended-release tablets discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events ($\geq 1\%$) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine hydrochloride extended-release tablets compared to placebo) included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0%
Somnolence	1.4%	0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with paroxetine hydrochloride extended-release tablets discontinued due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	Placebo (n = 109)
Nausea	2.9%	0%
Headache	1.9%	0.9%
Depression	1.9%	0%
LFT's abnormal	1.9%	0%

Panic Disorder

Eleven percent (50/444) of patients treated with paroxetine hydrochloride extended-release tablets in panic disorder studies discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

Paroxetine

Placebo

**Hydrochloride
Extended-Release
Tablets
(n = 444)**

Nausea	2.9%	(n = 445) 0.4%
Insomnia	1.8%	0%
Headache	1.4%	0.2%
Asthenia	1.1%	0%

Social Anxiety Disorder

Three percent (5/186) of patients treated with paroxetine hydrochloride extended-release tablets in the social anxiety disorder study discontinued treatment due to an adverse event. Events meeting the above criteria included the following:

**Paroxetine
Hydrochloride
Extended-Release
Tablets
(n = 186)**

Nausea	2.2%	Placebo (n = 184) 0.5%
Headache	1.6%	0.5%
Diarrhea	1.1%	0.5%

Premenstrual Dysphoric Disorder

Spontaneously reported adverse events were monitored in studies of both continuous and intermittent dosing of paroxetine hydrochloride extended-release tablets in the treatment of PMDD. Generally, there were few differences in the adverse event profiles of the two dosing regimens. Thirteen percent (88/681) of patients treated with paroxetine hydrochloride extended-release tablets in PMDD studies of continuous dosing discontinued treatment due to an adverse event.

The most common events ($\geq 1\%$) associated with discontinuation in either group treated with paroxetine hydrochloride extended-release tablets with an incidence rate that is at least twice that of placebo in PMDD trials that employed a continuous dosing regimen are shown in the following table. This table also shows those events that were dose dependent (indicated with an asterisk) as defined as events having an incidence rate with 25 mg of paroxetine hydrochloride extended-release tablets that was at least twice that with 12.5 mg of paroxetine hydrochloride extended-release tablets (as well as the placebo group).

	Paroxetine Hydrochloride Extended-Release Tablets 25 mg (n = 348)	Paroxetine Hydrochloride Extended-Release Tablets 12.5 mg (n = 333)	Placebo (n = 349)
TOTAL	15%	9.9%	6.3%
Nausea*	6%	2.4%	0.9%
Asthenia	4.9%	3%	1.4%
Somnolence*	4.3%	1.8%	0.3%
Insomnia	2.3%	1.5%	0%
Concentration Impaired*	2%	0.6%	0.3%
Dry mouth*	2%	0.6%	0.3%
Dizziness*	1.7%	0.6%	0.6%
Decreased Appetite*	1.4%	0.6%	0%
Sweating*	1.4%	0%	0.3%
Tremor*	1.4%	0.3%	0%
Yawn*	1.1%	0%	0%
Diarrhea	0.9%	1.2%	0%

Events considered to be dose dependent are defined as events having an incidence rate with 25 mg of paroxetine hydrochloride extended-release tablets that was at least twice that with 12.5 mg of paroxetine hydrochloride extended-release tablets (as well as the placebo group).

Commonly Observed Adverse Events

Major Depressive Disorder

The most commonly observed adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a pool of two trials (incidence of 5% or greater and incidence for paroxetine hydrochloride extended-release tablets at least twice that for placebo, derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor and yawning.

Using the same criteria, the adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating and tremor.

Panic Disorder

In the pool of panic disorder studies, the adverse events meeting these criteria were: Abnormal ejaculation, somnolence, impotence, libido decreased, tremor, sweating and female genital disorders (generally anorgasmia or difficulty achieving orgasm).

Social Anxiety Disorder

In the social anxiety disorder study, the adverse events meeting these criteria were: Nausea, asthenia, abnormal ejaculation, sweating, somnolence, impotence, insomnia and libido decreased.

Premenstrual Dysphoric Disorder

The most commonly observed adverse events associated with the use of paroxetine hydrochloride extended-release tablets either during continuous dosing or luteal phase dosing (incidence of 5% or greater and incidence for paroxetine hydrochloride extended-release tablets at least twice that for placebo, derived from Table 6) were: Nausea, asthenia, libido decreased, somnolence, insomnia, female genital disorders, sweating, dizziness, diarrhea and constipation.

In the luteal phase dosing PMDD trial, which employed dosing of 12.5 mg/day or 25 mg/day of paroxetine hydrochloride extended-release tablets limited to the 2 weeks prior to the onset of menses over 3 consecutive menstrual cycles, adverse events were evaluated during the first 14 days of each off-drug phase. When the three off-drug phases were combined, the following adverse events were reported at an incidence of 2% or greater for paroxetine hydrochloride extended-release tablets and were at least twice the rate of that reported for placebo: Infection (5.3% versus 2.5%), depression (2.8% versus 0.8%), insomnia (2.4% versus 0.8%), sinusitis (2.4% versus 0%) and asthenia (2% versus 0.8%).

Incidence in Controlled Clinical Trials

Table 2 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with paroxetine hydrochloride extended-release tablets, aged 18 to 65, who participated in two short-term (12 week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with paroxetine hydrochloride extended-release tablets who participated in short-term (10 week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day. Table 6 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with paroxetine hydrochloride extended-release tablets who participated in three, 12-week, placebo-controlled trials in PMDD in which patients were dosed at 12.5 mg/day or 25 mg/day and in one 12-week placebo-controlled trial in which patients were dosed for 2 weeks prior to the onset of menses (luteal phase dosing) at 12.5 mg/day or 25 mg/day. Reported adverse events were classified using a standard COSTART-based Dictionary terminology.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 2. Treatment Emergent Adverse Events Occurring in $\geq 1\%$ of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Two Studies in Major Depressive Disorder^{*†}

Body System/Adverse Event	% Reporting Event	
	Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	Placebo (n = 211)
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection [‡]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma [§]	5%	1%
Pain [¶]	3%	1%
Allergic Reaction [#]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation ^p	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%

Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision ^ß	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation ^{àè}	26%	1%
Female Genital Disorder ^{àð}	10%	<1%
Impotence ^à	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder ^à	2%	<1%
Vaginitis ^à	2%	0%

*Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency and weight gain.

†< 1% means greater than zero and less than 1%.

‡Mostly flu.

§A wide variety of injuries with no obvious pattern.

¶Pain in a variety of locations with no obvious pattern.

#Most frequently seasonal allergic symptoms.

•Usually flushing.

ßMostly blurred vision.

àBased on the number of males or females.

èMostly anorgasmia or delayed ejaculation.

ðMostly anorgasmia or delayed orgasm.

Table 3. Treatment Emergent Adverse Events Occurring in ≥ 5% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Study of Elderly Patients with Major Depressive Disorder ^{*†}

Body System/Adverse Event	% Reporting Event	
	Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	Placebo (n = 109)
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%

Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	<1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	<1%
Urogenital System		
Abnormal Ejaculation ^{‡§}	17%	3%
Impotence [‡]	9%	3%

*Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.

†< 1% means greater than zero and less than 1%.

‡Based on the number of males.

§Mostly anorgasmia or delayed ejaculation.

Table 4. Treatment Emergent Adverse Events Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Three Panic Disorder Studies^{*†}

Body System/Adverse Event	% Reporting Event	
	Paroxetine Hydrochloride Extended-Release Tablets (n = 444)	Placebo (n = 445)
Body as a Whole		
Asthenia	15%	10%
Abdominal Pain	6%	4%
Trauma [†]	5%	4%
Cardiovascular System		
Vasodilation [§]	3%	2%
Digestive System		
Nausea	23%	17%
Dry Mouth	13%	9%
Diarrhea	12%	9%
Constipation	9%	6%
Decreased Appetite	8%	6%
Metabolic/Nutritional Disorders		
Weight Loss	1%	0%
Musculoskeletal System		
Myalgia	5%	3%

Nervous System		
Insomnia	20%	11%
Somnolence	20%	9%
Libido Decreased	9%	4%
Nervousness	8%	7%
Tremor	8%	2%
Anxiety	5%	4%
Agitation	3%	2%
Hypertonia [¶]	2%	<1%
Myoclonus	2%	<1%
Respiratory System		
Sinusitis	8%	5%
Yawn	3%	0%
Skin and Appendages		
Sweating	7%	2%
Special Senses		
Abnormal Vision [#]	3%	<1%
Urogenital System		
Abnormal Ejaculation ^{ⒶⒷ}	27%	3%
Impotence [Ⓐ]	10%	1%
Female Genital Disorders ^{ⒶⒺ}	7%	1%
Urinary Frequency	2%	<1%
Urination Impaired	2%	<1%
Vaginitis [Ⓐ]	1%	<1%

*Adverse events for which the reporting rate for paroxetine hydrochloride extended-release tablets was less than or equal to the placebo rate are not included. These events are: Abnormal dreams, allergic reaction, back pain, bronchitis, chest pain, concentration impaired, confusion, cough increased, depression, dizziness, dysmenorrhea, dyspepsia, fever, flatulence, headache, increased appetite, infection, menstrual disorder, migraine, pain, paresthesia, pharyngitis, respiratory disorder, rhinitis, tachycardia, taste perversion, thinking abnormal, urinary tract infection and vomiting.

†< 1% means greater than zero and less than 1%.

‡Various physical injuries.

§Mostly flushing.

¶Mostly muscle tightness or stiffness.

#Mostly blurred vision.

ⒶBased on the number of male patients.

ⒷMostly anorgasmia or delayed ejaculation.

ⒶBased on the number of female patients.

ⒺMostly anorgasmia or difficulty achieving orgasm.

Table 5. Treatment Emergent Adverse Effects Occurring in ≥ 1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Social Anxiety Disorder Study^{*†}

Body System/Adverse Event	% Reporting Event	
	Paroxetine Hydrochloride Extended-Release Tablets	Placebo (n = 184)

	(n = 186)	
Body as a Whole		
Headache	23%	17%
Asthenia	18%	7%
Abdominal Pain	5%	4%
Back Pain	4%	1%
Trauma [‡]	3%	<1%
Allergic Reaction [§]	2%	<1%
Chest Pain	1%	<1%
Cardiovascular System		
Hypertension	2%	0%
Migraine	2%	1%
Tachycardia	2%	1%
Digestive System		
Nausea	22%	6%
Diarrhea	9%	8%
Constipation	5%	2%
Dry Mouth	3%	2%
Dyspepsia	2%	<1%
Decreased Appetite	1%	<1%
Tooth Disorder	1%	0%
Metabolic/Nutritional Disorders		
Weight Gain	3%	1%
Weight Loss	1%	0%
Nervous System		
Insomnia	9%	4%
Somnolence	9%	4%
Libido Decreased	8%	1%
Dizziness	7%	4%
Tremor	4%	2%
Anxiety	2%	1%
Concentration Impaired	2%	0%
Depression	2%	1%
Myoclonus	1%	<1%
Paresthesia	1%	<1%
Respiratory System		
Yawn	2%	0%
Skin and Appendages		
Sweating	14%	3%
Eczema	1%	0%
Special Senses		
Abnormal Vision [¶]	2%	0%
Abnormality of Accommodation	2%	0%
Urogenital System		
Abnormal Ejaculation ^{#P}	15%	1%
Impotence [#]	9%	0%
Female Genital Disorders ^{‡à}	3%	0%

*Adverse events for which the reporting rate for paroxetine hydrochloride extended-release tablets was less than or equal to the placebo rate are not included. These events are: Dysmenorrhea, flatulence, gastroenteritis, hypertonia, infection, pain, pharyngitis, rash, respiratory disorder, rhinitis, and vomiting.

†< 1% means greater than zero and less than 1%.

‡Various physical injuries.

§Most frequently seasonal allergic symptoms.

¶Mostly blurred vision.

#Based on the number of male patients.

♂Mostly anorgasmia or delayed ejaculation.

♀Based on the number of female patients.

♂♂Mostly anorgasmia or difficulty achieving orgasm.

Table 6. Treatment-Emergent Adverse Events Occurring in > 1% of Patients Treated With Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Three Premenstrual Dysphoric Disorder Studies with Continuous Dosing or in One Premenstrual Dysphoric Disorder Study with Luteal Phase Dosing^{*†‡}

Body System/ Adverse Event	% Reporting Event			
	Continuous Dosing		Luteal Phase Dosing	
	Paroxetine Hydrochloride Extended- Release Tablets (n = 681)	Placebo (n = 349)	Paroxetine Hydrochloride Extended-Release Tablets (n = 246)	Placebo (n = 120)
Body as a Whole				
Asthenia	17%	6%	15%	4%
Headache	15%	12%	-	-
Infection	6%	4%	-	-
Abdominal pain	-	-	3%	0%
Cardiovascular System				
Migraine	1%	< 1%	-	-
Digestive System				
Nausea	17%	7%	18%	2%
Diarrhea	6%	2%	6%	0%
Constipation	5%	1%	2%	< 1%
Dry Mouth	4%	2%	2%	< 1%
Increased Appetite	3%	< 1%	-	-
Decreased Appetite	2%	< 1%	2%	0%
Dyspepsia	2%	1%	2%	2%
Gingivitis	-	-	1%	0%
Metabolic and Nutritional Disorders				
Generalized Edema	-	-	1%	< 1%
Weight Gain	-	-	1%	< 1%

Musculoskeletal System				
Arthralgia	2%	1%	-	-
Nervous System				
Libido Decreased	12%	5%	9%	6%
Somnolence	9%	2%	3%	< 1%
Insomnia	8%	2%	7%	3%
Dizziness	7%	3%	6%	3%
Tremor	4%	< 1%	5%	0%
Concentration Impaired	3%	< 1%	1%	0%
Nervousness	2%	< 1%	3%	2%
Anxiety	2%	1%	-	-
Lack of Emotion	2%	< 1%	-	-
Depression	-	-	2%	< 1%
Vertigo	-	-	2%	< 1%
Abnormal Dreams	< 1%	< 1%	-	-
Amnesia	-	-	1%	0%
Respiratory System				
Sinusitis	-	-	4%	2%
Yawn	2%	< 1%	-	-
Bronchitis	-	-	2%	0%
Cough Increased	1%	< 1%	-	-
Skin and Appendages				
Sweating	7%	< 1%	6%	< 1%
Special Senses				
Abnormal Vision	-	-	1%	0%
Urogenital System				
Female Genital Disorders [§]	8%	1%	2%	0%
Menorrhagia	1%	1%	-	-
Vaginal Moniliasis	1%	1%	-	-
Menstrual Disorder	-	-	1%	0%

*Adverse events for which the reporting rate of paroxetine hydrochloride extended-release tablets was less than or equal to the placebo rate are not included. These events for continuous dosing are: Abdominal pain, back pain, pain, trauma, weight gain, myalgia, pharyngitis, respiratory disorder, rhinitis, sinusitis, pruritis, dysmenorrhea, menstrual disorder, urinary tract infection and vomiting. The events for luteal phase dosing are: Allergic reaction, back pain, headache, infection, pain, trauma, myalgia, anxiety, pharyngitis, respiratory disorder, cystitis and dysmenorrhea.

†<1% means greater than zero and less than 1%.

‡The luteal phase and continuous dosing PMDD trials were not designed for making direct comparisons between the two dosing regimens. Therefore, a comparison between the two dosing regimens of the PMDD trials of incidence rates shown in Table 5 should be avoided.

§

Mostly anorgasmia or difficulty achieving orgasm.

Dose Dependency of Adverse Events

The following table shows results in PMDD trials of common adverse events, defined as events with an incidence of $\geq 1\%$ with 25 mg of paroxetine hydrochloride extended release tablets that was at least twice that with 12.5 mg of paroxetine hydrochloride extended release tablets and with placebo.

Incidence of Common Adverse Events in Placebo, 12.5 mg and 25 mg of Paroxetine Hydrochloride Extended-release Tablets in a Pool of Three Fixed-Dose PMDD Trials

Common Adverse Event	Paroxetine Hydrochloride Extended-Release Tablets 25 mg (n = 348)	Paroxetine Hydrochloride Extended-Release Tablets 12.5 mg (n = 333)	Placebo (n = 349)
Sweating	8.9%	4.2%	0.9%
Tremor	6%	1.5%	0.3%
Concentration Impaired	4.3%	1.5%	0.6%
Yawn	3.2%	0.9%	0.3%
Paresthesia	1.4%	0.3%	0.3%
Hyperkinesia	1.1%	0.3%	0%
Vaginitis	1.1%	0.3%	0.3%

A comparison of adverse event rates in a fixed dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

Male and Female Sexual Dysfunction with SSRIs

Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences.

Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance and satisfaction are difficult to obtain; however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling, are likely to underestimate their actual incidence.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of two placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of three placebo-controlled trials in patients with panic disorder, in the placebo-controlled trial in patients with social anxiety disorder and in the intermittent dosing and the pool of three placebo-controlled continuous dosing trials in female patients with PMDD are as follows:

	Major Depressive Disorder		Panic Disorder		Social Anxiety Disorder		PMDD Continuous Dosing		PMDD Luteal Phase Dosing	
	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo	Paroxetine HCl Extended-Release Tablets	Placebo
n (males)	78	78	162	194	88	97	n/a	n/a	n/a	n/a
Decreased Libido	10%	5%	9%	6%	13%	1%	n/a	n/a	n/a	n/a
Ejaculatory Disturbance	26%	1%	27%	3%	15%	1%	n/a	n/a	n/a	n/a
Impotence	5%	3%	10%	1%	9%	0%	n/a	n/a	n/a	n/a
n (females)	134	133	282	251	98	87	681	349	246	120
Decreased Libido	4%	2%	8%	2%	4%	1%	12%	5%	9%	6%
Orgasmic Disturbance	10%	<1%	7%	1%	3%	0%	8%	1%	2%	0%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects.

Weight and Vital Sign Changes

Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with paroxetine hydrochloride extended-release tablets or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse and temperature) were observed in patients treated with paroxetine hydrochloride extended-release tablets or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes

In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests

In a pool of two placebo-controlled clinical trials, patients treated with paroxetine hydrochloride extended-release tablets or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the extended-release paroxetine versus placebo comparisons for alkaline phosphatase, SGOT, SGPT and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with paroxetine hydrochloride extended-release tablets and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with paroxetine hydrochloride extended-release tablets dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, 4 of 444 patients treated with paroxetine hydrochloride extended-release tablets and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of paroxetine hydrochloride extended-release tablets. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations

In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine

The following adverse events were reported during the clinical development of paroxetine hydrochloride extended-release tablet and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the extended-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder, social anxiety disorder and PMDD, multiple doses of paroxetine hydrochloride extended-release tablets were administered to 1,627 patients in phase three double-blind, controlled, outpatient studies. Untoward events associated with this exposure were recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to paroxetine hydrochloride extended-release tablets who experienced an event of the type cited on at least one occasion while receiving paroxetine hydrochloride extended-release tablets. All reported events are included except those already listed in Tables 2 through 6 and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase two and three studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder and posttraumatic stress disorder. The conditions and duration of exposure to immediate-release

paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies and fixed dose and titration studies. Only those events not previously listed for extended-release paroxetine are included. The extent to which these events may be associated with paroxetine hydrochloride extended-release tablets is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesterolemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, nonprotein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction, manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea¹; infrequent were albuminuria, amenorrhea¹, breast pain¹, cystitis, dysuria, prostatitis¹, urinary retention; rare were breast enlargement¹, breast neoplasm¹, female lactation, hematuria, kidney calculus, metrorrhagia¹, nephritis, nocturia, pregnancy and puerperal disorders¹, salpingitis, urinary incontinence, uterine fibroids enlarged¹; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

1

Based on the number of men and women as appropriate.

Post-Marketing Reports

Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis and grossly elevated transaminases associated with severe liver

dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including Torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia and agranulocytosis) and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class

Paroxetine hydrochloride is not a controlled substance.

Physical and Psychologic Dependence

Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS active drug will be misused, diverted and/or abused once marketed. Consequently, patients should be evaluated carefully for history of drug abuse and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE

Human Experience

Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure and urinary retention.

Overdosage Management

Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: Drugs Metabolized by Cytochrome CPY2D6).

In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION

Major Depressive Disorder

Usual Initial Dosage

Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed and should be swallowed whole.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics).

Panic Disorder

Usual Initial Dosage

Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning. Patients should be started on 12.5 mg/day. Dose changes should occur in 12.5 mg/day increments and at intervals of at least one week. Patients were dosed in a range of 12.5 to 75 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets. The maximum dosage should not exceed 75 mg/day.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed and should be swallowed whole.

Maintenance Therapy

Long-term maintenance of efficacy with the immediate-release formulation of paroxetine was demonstrated in a 3 month relapse prevention trial. In this trial, patients with panic disorder assigned to immediate-release paroxetine demonstrated a lower relapse rate compared to patients on placebo. Panic disorder is a chronic condition and it is reasonable to consider continuation for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Social Anxiety Disorder

Usual Initial Dosage

Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 12.5 mg/day. Patients were dosed in a range of 12.5 mg to 37.5 mg/day in the clinical trial demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of social anxiety disorder. If the dose is increased, this should occur at intervals of at least one week, in increments of 12.5 mg/day, up to a maximum of 37.5 mg/day.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed and should be swallowed whole.

Maintenance Therapy

There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. Although the efficacy of paroxetine hydrochloride extended-release tablets beyond 12 weeks of dosing has not been demonstrated in controlled clinical trials, social anxiety disorder is recognized as a chronic condition and it is reasonable to consider continuation of treatment for a responding patient. Dosage adjustments should be made to maintain the patient on the lowest effective dosage and patients should be periodically reassessed to determine the need for continued treatment.

Premenstrual Dysphoric Disorder

Usual Initial Dosage

Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. Paroxetine hydrochloride extended-release tablets may be administered either daily throughout the menstrual cycle or limited to the luteal phase of the menstrual cycle, depending on physician assessment. The recommended initial dose is 12.5 mg/day. In clinical trials, both 12.5 mg/day and 25 mg/day were shown to be effective. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed and should be swallowed whole.

Maintenance/Continuation Therapy

The effectiveness of Paroxetine hydrochloride extended-release tablets for a period exceeding three menstrual cycles has not been systematically evaluated in controlled trials. However, women commonly report that symptoms worsen with age until relieved by the onset of menopause. Therefore, it is reasonable to consider continuation of a responding patient. Patients should be periodically reassessed to determine the need for continued treatment.

Special Populations

Treatment of Pregnant Women During the Third Trimester

Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients and Patients with Severe Renal or Hepatic Impairment

The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor

At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets

Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED

Paroxetine Hydrochloride Extended-release Tablets are available as 12.5 mg and 25 mg tablets.

The 12.5 mg tablet is a white film-coated, round, unscored tablet with M over P3 imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-2003-93

bottles of 30 tablets

NDC 0378-2003-01

bottles of 100 tablets

NDC 0378-2003-05

bottles of 500 tablets

The 25 mg tablet is a lavender film-coated, round, unscored tablet with M over P4 imprinted in black ink on one side of the tablet and blank on the other side. They are available as follows:

NDC 0378-2004-93

bottles of 30 tablets

NDC 0378-2004-01

bottles of 100 tablets

NDC 0378-2004-05

bottles of 500 tablets

Store at 20° to 25 °C (68° to 77°F). [See USP Controlled Room Temperature.]

Dispense in a tight, light-resistant container as defined in the USP using a child-resistant closure.

PHARMACIST: Dispense a Medication Guide with each prescription.

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505

REVISED August 2009

PRXT:R7mc

MEDICATION GUIDE ANTIDEPRESSANT MEDICINES, DEPRESSION AND OTHER SERIOUS MENTAL ILLNESSES, AND SUICIDAL THOUGHTS OR ACTIONS

Read the Medication Guide that comes with your or your family member's antidepressant medicine. This Medication Guide is only about the risk of suicidal thoughts and actions with antidepressant medicines. Talk to your, or your family member's, healthcare provider about:

- all risks and benefits of treatment with antidepressant medicines
- all treatment choices for depression or other serious mental illness

What is the most important information I should know about antidepressant medicines, depression and other serious mental illnesses, and suicidal thoughts or actions?

1. Antidepressant medicines may increase suicidal thoughts or actions in some children, teenagers, and young adults within the first few months of treatment.
2. Depression and other serious mental illnesses are the most important causes of suicidal thoughts and actions. Some people may have a particularly high risk of having suicidal thoughts or actions. These include people who have (or have a family history of) bipolar illness (also called manic-depressive illness) or suicidal thoughts or actions.
3. How can I watch for and try to prevent suicidal thoughts and actions in myself or a family member?
 - # Pay close attention to any changes, especially sudden changes, in mood, behaviors, thoughts, or feelings. This is very important when an antidepressant medicine is started or when the dose is changed.
 - # Call the healthcare provider right away to report new or sudden changes in mood, behavior, thoughts, or feelings.
 - # Keep all follow-up visits with the healthcare provider as scheduled. Call the healthcare provider between visits as needed, especially if you have concerns about symptoms.

Call a healthcare provider right away if you or your family member has any of the following symptoms, especially if they are new, worse, or worry you:

- thoughts about suicide or dying
- attempts to commit suicide
- new or worse depression
- new or worse anxiety
- feeling very agitated or restless
- panic attacks
- trouble sleeping (insomnia)
- new or worse irritability
- acting aggressive, being angry, or violent
- acting on dangerous impulses
- an extreme increase in activity and talking (mania)
- other unusual changes in behavior or mood

What else do I need to know about antidepressant medicines?

- Never stop an antidepressant medicine without first talking to a healthcare provider. Stopping an antidepressant medicine suddenly can cause other symptoms.

- Antidepressants are medicines used to treat depression and other illnesses. It is important to discuss all the risks of treating depression and also the risks of not treating it. Patients and their families or other caregivers should discuss all treatment choices with the healthcare provider, not just the use of antidepressants.
- Antidepressant medicines have other side effects. Talk to the healthcare provider about the side effects of the medicine prescribed for you or your family member.
- Antidepressant medicines can interact with other medicines. Know all of the medicines that you or your family member takes. Keep a list of all medicines to show the healthcare provider. Do not start new medicines without first checking with your healthcare provider.
- Not all antidepressant medicines prescribed for children are FDA approved for use in children. Talk to your child's healthcare provider for more information.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

This Medication Guide has been approved by the U.S. Food and Drug Administration for all antidepressants.

Revised 1/2008

PRINCIPAL DISPLAY PANEL - 12.5 mg

NDC 0378-2003-93

PAROXETINE

HYDROCHLORIDE

EXTENDED-RELEASE

TABLETS

12.5 mg*

**PHARMACIST: PLEASE DISPENSE WITH
MEDICATION GUIDE PROVIDED SEPARATELY.**

30 TABLETS (Rx only)

*Each film-coated tablet

contains paroxetine

hydrochloride, USP equivalent

to 12.5 mg of paroxetine.

Dispense in a tight, light-resistant

container as defined in the USP

using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

Store at 20° to 25°C (68° to 77°F).

**[See USP Controlled Room
Temperature.]**

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505

RM2003H2



PRINCIPAL DISPLAY PANEL - 25 mg

NDC 0378-2004-93

**PAROXETINE
HYDROCHLORIDE
EXTENDED-RELEASE
TABLETS**

25 mg*

**PHARMACIST: PLEASE DISPENSE WITH
MEDICATION GUIDE PROVIDED SEPARATELY.**

30 TABLETS (Rx only)

*Each film-coated tablet

contains paroxetine
hydrochloride, USP equivalent
to 25 mg of paroxetine.

Dispense in a tight, light-resistant
container as defined in the USP
using a child-resistant closure.

Keep container tightly closed.

**Keep this and all medication
out of the reach of children.**

Store at 20° to 25°C (68° to 77°F).

**[See USP Controlled Room
Temperature.]**

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.

Morgantown, WV 26505

RM2004H2

The image shows a white rectangular medication label with black and green text, set against a blue background. On the left, there is a vertical barcode with the numbers '3 0378-2004-93 9' printed vertically. To the right of the barcode, the text '25 mg*' is printed vertically. The main body of the label contains the following information: 'NDC 0378-2004-93' at the top right; 'MYLAN®' logo and 'PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 25 mg*' in green and black text; a box containing 'PHARMACIST: PLEASE DISPENSE WITH MEDICATION GUIDE PROVIDED SEPARATELY.' and '30 TABLETS' with an 'Rx only' symbol; and detailed storage and usage instructions on the right side. The label is bordered by a thin black line.

3 0378-2004-93 9

25 mg*

NDC 0378-2004-93

MYLAN®

**PAROXETINE
HYDROCHLORIDE
EXTENDED-RELEASE
TABLETS**

25 mg*

PHARMACIST: PLEASE DISPENSE WITH
MEDICATION GUIDE PROVIDED SEPARATELY.

30 TABLETS

Rx only

Dispense in a tight, light-resistant
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using a child-resistant closure.

Keep container tightly closed.

Keep this and all medication
out of the reach of children.

Store at 20° to 25°C (68° to 77°F).
[See USP Controlled Room
Temperature.]

Usual Dosage: See accompanying
prescribing information.

Mylan Pharmaceuticals Inc.
Morgantown, WV 26505

RM2004H2